



Situation Update

The Ongoing Monkeypox Pandemic

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Summary:

On August 16, 2024, for the second recent time, the World Health Organization (WHO) declared the ongoing outbreak of monkeypox (mpox; MPXV) as a global public health emergency. This was after the African Centers for Disease Control and Prevention logged over 15,000 reported cases of mpox earlier this week, primarily in the Democratic Republic of the Congo (DRC). Human mpox cases have been regularly recorded in the Congo since 1970, although it was originally discovered in 1958 in Denmark in crab-eating macaque monkeys used for research.¹ Until the 2022 global outbreak, mpox cases were quite rare outside of Central and West Africa. With the most recent outbreak, at least 15 countries in Africa as well as Pakistan and Sweden have reported mpox infections. Attenuated, live preparations of smallpox vaccines have been used to prevent mpox disease in high risk groups, and antiviral medications are available for treatment of symptomatic cases. Those that have been previously vaccinated against smallpox prior to 1980 have increased immunity to mpox disease.

The Mpox Virus

Mpox is a double-stranded DNA virus of the orthopoxvirus family, which includes smallpox (variola virus), cowpox, chickenpox and vaccinia virus. It is 96.3 percent identical in amino acid sequence to the variola virus in its gene coding regions. There are two clades of the mpox virus, with Clade 1 causing more serious illnesses and deaths (up to 10% of those who become ill) and endemic in Central Africa. Clade II is responsible for the 2022 global outbreak of mpox and is much more mild with greater than a 99.9% survival rate and endemic to West Africa. The two strains of present concern are 'Clade I' based, which include MPXV clade 1a and the new MPXV 1b variant that originally emerged around September 2023 in the DRC. The clade 1b variant appears to be more easily spread through routine close contact than other clade I viruses.

With a rounded brick-like structure caused by a dumbbell-shaped nucleocapsid, the mpox virus particle is more than 50-times larger in size than most other viruses such as SARS-CoV-2, influenza virus and human immunodeficiency virus (HIV). For example, mpox has a diameter of 200-250 nanometers, compared to a diameter of about 70-90 nanometers for spherical SARS-CoV-2 viral particles. The 197-kilobase genome of the mpox virus is linear, and encodes genes that specify about 191 different viral proteins.² The mpox genome is encapsulated within a lipid membrane along with enzymes that assist in entry and replication of the virus, which takes longer to reproduce inside of cells than most other viruses due to its large size. The specific human receptor that permits the binding and entry of the virus into host cells has not been identified, although viral envelope proteins appear to mediate entry by adhesion to glycosaminoglycans on the surface of cells.



The MPXV 1b variants features diverse mutations from earlier clade I members that results in about 158 amino acid changes across primarily seven of the mpox proteins, with acquisition of increased transmissibility.³ Dr. Bernie Moss is the Chief of the Genetic Engineering Section of the National Institute of Allergy and Infectious Diseases (NIAID) at the US National Institute of Health (NIH) in Bethesda, Maryland. Grant proposals submitted by Dr. Moss for funding from the NIH/NIAID proposed genetic gain-of-function research to increase the virulence of clade II variants using the transfer of genes from the more lethal clade I virus in research, but it is unclear whether this was ultimately funded.⁴ While it remains unknown how the MPXV 1b variants came about, it is likely that they arose naturally rather than by gain-of-function research and accidental release as many suspect has happened with SARS-CoV-2.

Mpox Disease Symptoms and Lethality

The mpox virus can cause fevers, rashes, lymphadenectasis (enlargement of lymph nodes) and extremely painful, boil-like skin lesions in its victims. Mpox has a typical incubation asymptomatic period of 6-13 days from exposure, but the illness phase can range from another 5-28 days in duration.

In the recent outbreak with about 16,700 reported cases in the DRC, there have been around 570 deaths, mostly in children under 15 years of age.⁵ The median age in the DRC is about 15.8 years, with a total population presently stands at around 109.76 million.⁶ It is unclear how many of the child fatalities were in children that were being trafficked or subjected to sexual abuse, but in view of the main means of transmission, this was likely a substantial fraction of these deaths. The DRC had the world's highest levels of verified cases of sexual violence against children committed by armed forces and armed groups in both 2021 and 2022, and this further increased by more than 40 percent in the first half of 2023.⁷

In 2023, there were some 1,145 cases and 7 fatalities from mpox in the DRC.⁸ By comparison in 2021, there were over 3.75 million cases of malaria in the DRC,⁹ which resulted in about 75,000 deaths, of which about 80% were in children under 5 years of age.¹⁰ Approximately 698,000 deaths in the DRC occurred from all causes in 2021.¹¹ Consequently, mpox represents a very tiny fraction of the deaths in the DRC, and other infectious diseases such as malaria, tuberculosis, pertussis, rubella and measles carry a much greater disease burden in the country. In 2022, in non-epidemic regions where sanitation, nutrition and medical care are better, the case fatality rate of mpox was much lower at about 1 in 2,500 (~0.04 percent).¹²



Those that are Most Vulnerable to Mpox

The latest strains of mpox have been suggested to have a case fatality rate of around 3.6 percent in adults and about double this in children.¹³ Generally, mpox cases are not life-threatening, but the most vulnerable for severe illness include people with severely compromised immune systems such as produced by HIV with acquired immunodeficiency syndrome (AIDS), people with a history of atopic dermatitis or eczema, pregnant women and children under 1 years of age. AIDS is particularly problematic in Africa. For example, in South Africa, it has been estimated that about 17.1 percent of those aged from 15 to 49 years have been infected with HIV in 2023, with rates as high as 62.3 percent in sex workers.¹⁴

The 2022 Mpox Pandemic

WHO Director-General Tedros Adhanom Ghebreyesus originally declared mpox as a global health emergency in 2022 after over 55,000 confirmed cases had been reported in 103 countries. Ultimately, about 100,000 people were infected world-wide. This declaration was not originally recommended by the scientific committee that was struck to review the available data at the time, but the committee was overruled by Mr. Ghebreyesus, who has no previous scientific or medical training or credentials.

A New England Journal of Medicine study of 528 mpox infections in 16 countries diagnosed between April 27 and June 24, 2022, found that:

“overall, 98% of the persons with infection were gay or bisexual men, 75% were White, and 41% had human immunodeficiency virus infection; the median age was 38 years. Transmission was suspected to have occurred through sexual activity in 95% of the persons with infection...Monkeypox virus DNA was detected in 29 of the 32 persons in whom seminal fluid was analyzed. Antiviral treatment was given to 5% of the persons overall, and 70 (13%) were hospitalized; the reasons for hospitalization were pain management, mostly for severe anorectal pain (21 persons); soft-tissue superinfection (18); pharyngitis limiting oral intake (5); eye lesions (2); acute kidney injury (2); myocarditis (2); and infection-control purposes (13). No deaths were reported.”¹⁵

Mpox tended not to produce illness in individuals over 50 years of age, apparently due to the lasting effects of previous smallpox vaccination.

The 2024 Mpox Pandemic

On August 19, 2024, the WHO announced a new “Public Health Emergency of International Concern (PHEIC)” for mpox, just before the previous one was set to expire on August 20, 2024.¹³

This time around, the selected committee members recommended the declaration of mpox as a pandemic of global concern and extended the PHEIC for another 12 months. The committee offered temporary recommendations for States Parties experiencing the upsurge of mpox cases, including, but not limited to, the DRC and Burundi, Kenya, Rwanda, and Uganda.

Mpox Transmission

Mpox usually spreads through very close, intimate physical contact. It is essentially a venereal disease that is most predominant in homosexual males. To protect oneself, close skin-to-skin contact with people who have rashes that are typical of mpox should be avoided. In particular, mpox is found in the rash caused by virus (scabs, crusts and pus) and infected body fluids, including respiratory secretions, and possibly urine and feces. The risk of infection from fomites (objects which can become infectious after being touched by an infected person) such as clothing or bedding is very low, but precautions should still be taken.

Following primarily skin-to-skin contact, the Mpox virus penetrates into tissues through mucous membranes (such as ocular, respiratory, oral, urethral, and rectal) or broken skin. During a latent period of up to two weeks that may be asymptomatic for the human host, the virus spreads throughout the body via tissue-resident immune cells and draining lymph nodes. Thereafter, rashes begin to appear from papules to vesicles and pustules, and eventually form crusts that heal, but may leave behind scars. Until the skin completely heals, the victim may be able to transmit the virus to others. The progressive rash phase typically lasts from 2 to 4 weeks.

Mpox is able to infect a wide range of animal hosts to permit its propagation. Consequently, it is also important to avoid interactions with animals that are infected with mpox virus. Such animals include monkeys, and small mammals such as rope and sun squirrels, giant-pouched rats and African dormice in West and Central Africa. These mammals are often asymptomatic, but are contagious when processed following hunting from body parts and fluids. Other species of animals that may become infected with mpox include anteaters, hedgehogs, prairie dogs, chinchillas and shrews, but apparently not birds, reptiles or amphibians. Pets such as dogs and cats were not found to be infected during the 2022 mpox pandemic.¹⁶

Mpox Vaccines

M-Pox vaccines are available, although there is a shortage in Africa, where most cases have been reported since the last major outbreak in 2022.

In 2022, the United States built a stockpile of approximately 20 million doses of the Barvarian Nordic's Jynneos (Imvamune) vaccine, a dual-purpose smallpox and Mpox vaccine.⁸ It is a live, attenuated, non-replicating, preparation of the smallpox virus.



The Jynneos Vaccine received Emergency Use Authorization from the FDA for “high risk” children under 18 years of age on August 13, 2022, after it was initially approved for those over 18 years of age in 2019.¹⁷ While clinical studies with the Jynneos vaccine were undertaken, there has not been a completed randomized clinical challenge trial so there are no clear data on its effectiveness for prevention of illness by mpox. However, somewhere between 1 in 90 to 1 in 6 of vaccine recipients, depending on the study, experienced elevated troponin levels or an abnormal EKG, which are indicative of heart damage.¹⁸ Remarkably, about 7% of HIV-positive, Jynneos vaccine recipients experienced side effects and a worsening of their HIV-symptoms. Subsequent studies by Deputy *et al.* (2023)¹⁹ in the US found with two doses of the Jynneos vaccine an estimated vaccine effectiveness of about 66% and 35.8% with one dose in preventing mpox.

In Canada, the Imvamune vaccine was approved for treatment of smallpox for persons 16 years of age and older at high risk, but is not recommended for the general population. Another live attenuated smallpox vaccine that has been approved is ACAM2000 from Emergent Bio Solutions Gaithersburg Inc., along with smallpox vaccine products from Sanofi Pasteur Ltd.²⁰

Treatment of Mpox

Tecovirimat (Tpox) is an intravenous and oral drug that is effective in the treatment of smallpox infections, and likely other orthopoxviruses such as, cowpox and mpox. It was approved by the US FDA in 2018.²¹ While it is fully approved for the treatment of smallpox in adults and children, based on animal efficacy data and safety data in 359 healthy adults, and it is presently in clinical trials as investigational drug for mpox. A wide range of other antiviral drugs for mpox are also in clinical development, which will increase the prospects for successful treatment of future mpox infections.²

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